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A Feasibility Study of UFT/LV and Irinotecan (TEGAFIRI) in Advanced or Metastatic Colorectal Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) PROG 0304

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Objective: This is a feasibility trial of oral uracil/tegafur (UFT)/oral leucovorin (LV) and irinotecan (TEGAFIRI) with maximum dose confirmed in Japan. To document the toxicity and define the objective response rate (RR); and determine progression-free and overall survival.
Methods: Patients with advanced or metastatic colorectal cancer (CRC) received: UFT 300 mg/m^2, LV 75 mg/body and CPT-11 150 mg/m^2 (UFT and LV given on days 1–14, and CPT-11 on day 1, every 3 weeks). Eligibility: ECOG performance status (PS) 0–1, adequate bone marrow/liver function and serum creatinine level less than institutional normal value.
Results: Eighteen patients enrolled, 17 evaluable for toxicity and response and 1 patients recalled chemotherapy upon registration. Characteristics: 61% male, median age 63.5 years (51–71). Seventy-two per cent PS 0, 50% first line. One hundred and eighty-six cycles have been delivered. The common Grade 3–4 toxicities were neutropenia (35.3%), leukopenia (29.4%), diarrhea (5.9%), anorexia (5.9%), vomiting (5.9%) and dizziness (5.9%). There was no episode of febrile neutropenia. No death occurred on treatment: Overall RR was 41.2% [7/17: 1 complete response (CR) + 6 partial response (PR)]. Progression-free survival (PFS) is 6.9 months, median survival time (MST) is 25.1 months and 1-year survival rate is 70.6%, whereas PFS 15.0 months, MST 43.6+ months and 1-year survival rate 100% in cases with CR or PR.
Conclusions: Approved dose of CPT-11 is 150 mg/m^2 in Japan. As is lower dose with CPT-11, TEGAFIRI for patients with advanced or metastatic CRC in Japan seems to have the similar effect with that reported abroad and indicates prolonged PFS and MST in cases with CR or PR.

Key words: colorectal cancer – chemotherapy – TEGAFIRI

INTRODUCTION

Combination chemotherapy of oxaliplatin and 5-fluorouracil (5-FU)/leucovorin (l-LV) (FOLFOX) or combination chemotherapy of CPT-11 and 5-FU/l-LV (FOLFIRI) has been used as standard regimens for advanced or metastatic colorectal cancer (CRC) in Japan. However, both regimens may have damage for patients' quality of life, because continuous infusion of 5-FU needs operation making central venous route or short hospitalization.

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It is reported that oral capecitabine had a strong trend for better survival than intravenous 5-FU/l-LV (1,2), and oral uracil/tegafur (UFT) plus oral leucovorin (LV) had the same survival as 5-FU–LV (3–5). Furthermore, combination chemotherapy of oxaliplatin and capecitabine is reported to be as effective as FOLFOX (6–8), combination chemotherapy of oxaliplatin and UFT/LV as FOLFOX (9), combination chemotherapy of CPT-11 and capecitabine as FOLFIRI (10), combination chemotherapy of CPT-11 and UFT/LV as FOLFIRI (9,11,12), whereas only UFT/LV and irinotecan (TEGAFIRI) is approved in Japan.

Two clinical studies were presented in Osaka Gastrointestinal Cancer Chemotherapy Study Group at the

start of TEGAFIRI. One is Phase I/II study to explore the efficacy and safety in patients with advanced/metastatic CRC (protocol no. 0303) and the other is feasibility study to explore the efficacy and safety of TEGAFIRI reported abroad with maximum dose approved in Japan (protocol no. 0304). This is a final report of the latter study.

PATIENTS AND METHODS

Patients

This study was approved by respective Institutional Review Board. The subjects were patients with advanced or recurrent CRC who fulfilled the following conditions: a measurable lesion meeting the response evaluation criteria in solid tumors (RECIST) with no history of radiation therapy, an age of $\leq$75 years, an ECOG performance status (PS) of 0–1, adequate function of major organs and no prior therapy with CPT-11. Other prior therapy, if any, had to be ceased at least 4 weeks before the study to avoid a carry-over effect.

Treatment

Subjects received CPT-11 (150 mg/m^2) on day 1, UFT (300 mg/m^2) on days 1–14 and LV (75 mg/day) on days 1–14 of each 21-day cycle. A steroid (equivalent to 8 mg of dexamethasone) and a 5-HT3 receptor antagonist (antiemetic) were administered to prevent CPT-11-induced nausea and vomiting. Subjects were defined as completing per protocol treatment when the following conditions were fulfilled on day 1 of the third cycle: delay of CPT-11 therapy by $\leq$7 days, missed UFT/LV treatment for $\leq$7 days, disappearance of similar toxicities following dose reduction, no Grade 3–4 increase in GOT or GPT, and a PS $\leq$ 2. Subjects were defined as withdrawing from treatment in any of the following cases: when treatment could not be completed, when an adverse event made it difficult to continue treatment, when disease progression occurred and when the subject wished to discontinue therapy.

Evaluation

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (Version 3.0), and their incidence and severity were determined.

To assess the antitumor effect, the response rate (RR) was defined as the percentage of evaluable patients whose best overall response was classified as either CR or PR according to the RECIST (13).

The progression-free survival (PFS) was calculated as the time from the first day of treatment to the first day of documented progression or death.

The survival time was defined as the time from the day of registration to the final date of confirmed survival or the date of death.

Statistical Analysis

The present study was conducted to evaluate the rate of completing treatment when UFT/LV was used in combination with CPT-11. Assuming that the expected completion rate is 80%, the accuracy is 20% and the threshold completion rate is 60%, a minimum of 16 evaluable patients would be required. In consideration of this number and possible ineligible patients and/or dropouts, the target number of patients for the present study was set at 18.

The Mann–Whitney U test was used for comparison between two independent groups and the log-rank test was used for comparison of survival. All statistical tests were two-tailed and $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Patient Characteristics

A total of 18 patients were enrolled in the study (Table 1). More than half of the patients were men (61%) and their ages ranged from 51 to 71 years. The PS was 0 in 72% of the patients and 50% had not received prior chemotherapy.

Table 1. Patient characteristics

Characteristics	
No. of patients	18
Age (years)	
Median	63.5
Range	51–71
Sex (%)	
Male	72.2
Female	27.8
ECOG performance status (%)	
0	61.1
1	38.9
Previous therapy (%)	
None	50
mFOLFOX6	5.6
5-FU derivatives	44.4
Tumor site (%)	
Colon	77.8
Rectum	22.2
Measurable lesions (%)	
Liver	44.4
Lymph nodes	38.9
Lung	11.1
Liver and lung	5.6

mFOLFOX, modified FOLFOX; 5-FU, 5-fluorouracil.

Fourteen patients had colon cancer (synchronous metastases in 10 patients and metachronous in 4 patients) and 4 patients had rectal cancer (synchronous metastases in 3 patients and metachronous in 1 patient) (patients who showed recurrence within 1 year of resection were classified as having synchronous metastasis).

There were measurable lesions of the liver in eight patients, lymph nodes in seven patients, lung in two patients, and both liver and lung in one patient.

Prior chemotherapy given within 6 months before the study was 5′-DFUR (doxifluridine) in three patients, UFT/LV in two patients, 5-FU/l-LV in one patient, S-1 (tegafur, gimeracil, oteracil potassium) in two patients and modified FOLFOX6 in one patient.

Treatment

One patient (63 years old with colon cancer for first-line treatment and a measurable lymph node metastasis) wished to change therapy after enrollment, so he received FOLFOX instead of TEGAFIRI. The remaining 17 patients received a total of 186 cycles of the present therapy (2–24 cycles per patient). Median dose intensity of CPT-11 was 83.8% and that of UFT was 81.1%.

One patient (a 66-year-old woman with rectal cancer for second-line treatment and a measurable lesion in the liver) did not complete therapy. The doses of CPT-11 and UFT were reduced because of Grade 3 leukopenia, Grade 3 neutropenia and Grade 3 anorexia, but similar adverse events occurred again. Therefore, treatment was discontinued on day 1 of the third cycle. Scheduled treatment could be continued in the remaining patients, so the treatment completions rate was 94.1% (16/17 patients).

One patient (a 58-year-old man with colon cancer for second-line treatment and a measurable lesion in the lung) underwent surgery. Because multiple nodules were observed in the lower lobe of the right lung during adjuvant chemotherapy, the patient selected chemotherapy first and the following operation if any other metastases were not seen in a few months. After completion of the second cycle, the response was rated as stable disease (SD), so curative resection was carried out at the patient's request.

From 6 to 24 cycles were administered to each responder, with a median number of 16 cycles. On the other hand, non-responders received two to eight cycles (except for a patient in whom the overall response was SD and 26 cycles were administered) and the median number of cycles for all non-responders was 5.

Subsequent chemotherapy was given to all 7 responders and 8 of the 10 non-responders. The percentage of responders undergoing subsequent treatment with FOLFOX was 57.1% (4/7 patients), whereas it was 71.4% for non-responders (5/7 patients, excluding 1 patient who had already received FOLFOX), and the rate was similar in the two groups ($P = 0.85$).

Toxicity

Dose reductions or treatment interruption for CPT-11 were needed for 29.4% of patients until day 1 of the third course and for 52.9% in all courses, and those for UFT were needed for none until day 1 of the third course and 29.4% in all courses.

Grade 3–4 adverse events (CTCAE Version 3.0) that occurred during treatment were neutropenia (35.3%), leukopenia (29.4%), diarrhea (5.9%), anorexia (5.9%), vomiting (5.9%) and dizziness (5.9%) (Table 2). There was no febrile neutropenia and no treatment-related death occurred.

Of the responders, only one experienced Grade 3–4 adverse events (Grade 3 leukopenia, Grade 4 neutropenia and Grade 3 diarrhea). In contrast, Grade 3–4 adverse events occurred in five non-responders, including three patients with SD and two patients with progressive disease (PD). There was no significant difference in the incidence of adverse events between responders and non-responders ($P = 0.29$).

Response

The best overall response was classified as CR in one patient, PR in six patients, SD in five patients, PD in four patients and not evaluable in one patient who underwent surgery. The RR was 41.2% (7/17 patients) (Table 3).

The RR achieved with first-line treatment was 37.5% (3/8 patients: 1 with CR and 2 with PR), whereas that for second-

Table 2. Frequency of common toxicities by the National Cancer Institute Common Toxicity Criteria (Version 3.0)

Toxicity	Highest grade/patient (%)		
	G0	G1 or G2	G3 or G4
Neutropenia	35.3	29.4	35.3
Leukopenia	41.2	29.4	29.4
Diarrhea	64.7	29.4	5.9
Anorexia	64.7	29.4	5.9
Vomiting	88.2	5.9	5.9
Dizziness	94.1	0	5.9

Table 3. Objective tumor response rates after external review

Best overall response	Patients (%)
Overall response rate	41.2
Complete response	5.9
Partial response	35.3
Stable disease	29.4
Progression	23.5
Not evaluable	5.9

Table 4. Prognostic factors

Outcome	Value
Median progression-free survival (months)	6.9
Median survival time (months)	25.1
One-year survival rate (%)	70.6

line treatment was 44.4% (4/9 patients: 4 with PR), i.e. a similar RR was achieved with second-line treatment ($P = 0.85$).

Complete response was achieved for a lung lesion, whereas PR was achieved for lymph node lesions in three patients, liver lesions in two patients, and both liver and lung lesions in one patient. No significant difference of response was noted among these sites ($P = 0.38$).

Survival

The median PFS was 6.9 months, the median survival time (MST) was 25.1 months and the 1-year survival rate was 70.6% (Table 4).

Responders had a median PFS of 15.0 months, MST of 43.6 months and 1-year survival rate of 100%, whereas the corresponding values for non-responders were 4 months, 10.6 months and 44.4%, respectively.

DISCUSSION

In the present study of TEGAFIRI, we employed the regimen that is widely used outside Japan. In this regimen, parenteral treatment is administered every 3 weeks in combination with 2 weeks of oral medication followed by a 1-week rest, and it is considered to be also applicable for use in Japan. Although the dose is set at 240–250 mg/m^2 for CPT-11 and 90 mg/day for LV when TEGAFIRI is given outside Japan (9,11,12), it was reduced to 150 mg/m^2 for CPT-11 and 75 mg/day for LV owing to restrictions imposed by the national health insurance scheme in Japan. For UFT, in contrast, the daily dose is 250 mg/m^2 outside Japan (9,11,12), whereas 300 mg/m^2/day (the standard domestic dosage) was used in the present study because the dose-limiting toxicity of diarrhea is less likely to occur in Orientals (5).

Although the dose of CPT-11 was lower in the present study than in overseas studies, the RR was similar in both cases. Polymorphism of the gene for UGT1A1, an enzyme participating in the metabolism of irinotecan, might lead to ethnic differences in the metabolism of this agent.

The incidence of Grade 3–4 adverse events showed lower tendency in responders than in non-responders ($P = 0.29$). This suggests that much efficacy cannot be expected in patients experiencing frequent adverse events.

In the present study, second-line treatment with TEGAFIRI achieved a similar effect to first-line treatment. Among the patients who received TEGAFIRI as second-line treatment, only one had received FOLFOX as first-line treatment and the others had been treated with 5-FU derivatives.

In the present study, the median PFS was 6.9 months and the MST was 25.1 months. These results are similar to the corresponding data reported for FOLFOX therapy (8.0 and 20.6 months) and for FOLFIRI therapy (8.5 and 21.5 months) (14). In the present study, the responders achieved a satisfactory outcome, with a median PFS of 15.0 months and an MST of 43.6 months. This outcome may have been achieved because the dose and regimen used in the present study were optimal, so that adverse events did not force patients to suspend treatment.

Now, the initial treatment for patients with advanced or recurrent CRC was FOLFIRI or FOLFOX in Japan. However, TEGAFIRI is one of the effective regimens for those who reject or cannot be performed continuous infusion of 5-FU or the operation of making central venous route. Further study on bevacizumab in combination with TEGAFIRI for patients with advanced or recurrent CRC is in preparation.

Dosages for Japanese patients should generally be determined on the basis of the results of Phase I trials conducted in Japan. For some drugs, however, we can also employ the large amounts of overseas data already obtained from more than one ethnic group. Therefore, it may be advisable to introduce overseas protocols for domestic clinical trials with the aid of overseas data, as was done in the present study.

In conclusion, the dose of CPT-11 approved in Japan is only 150 mg/m^2, but the RR obtained with TEGAFIRI using this dose was comparable to that obtained with full-dose TEGAFIRI outside Japan, and the responders achieved a good PFS of 15.0 months and an MST of 43.6 months.

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Conflict of interest statement

None declared.

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